Chapter 13
Exercise and Diet in the Control of Inflammation and Pain

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Abstract Lifestyle choices, such as exercise and diet, can play significant roles in mediating inflammation and consequently, pain. Functional medicine is an emerging medical specialty that focuses on lifestyle influences, genetics, and the environment to determine what is causing disease or chronic conditions such as chronic pain. The foundation of functional medicine is the use of food as a first-line therapy. The right nutrition, combined with the right lifestyle and behavioral interventions, will help individuals take charge of their health. Healthy diets are enriched with omega-3 unsaturated fatty acids, such as DHA (docosahexaenoic acid) and EPA (eicosapentaenoic acid). These are precursors of specialized proresolving mediators (SPMs) which are known to potently inhibit pain in various animal models of inflammation. Exercise can profoundly change immune cell phenotypes and promote the resolution of inflammation and pain. In particular, a combination of exercise and a healthy diet can facilitate the biosynthesis of SPMs from DHA and EPA, generating synergistic health benefits.

Keywords Inflammation · Chronic pain · COVID-19 · Diet · Exercise · Exerkines · Functional medicine · Myokines · Omega-3 unsaturated fatty acids · Specialized proresolving mediators (SPMs) · Resolution of inflammation

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13.1 Introduction

Behavior change cannot be picked up at the pharmacy and taken twice daily. As a result, exercise and diet are often overlooked in the management of pain in favor of pharmacological, interventional, or surgical treatments. Nonetheless, exercise and diet can have consequential roles in helping to reduce inflammation and attenuate pain. Functional medicine is an emerging specialty that focuses on lifestyle influences, genetics, and the environment to determine what is causing disease or chronic conditions such as chronic pain. The foundation of functional medicine is that lifestyle and behavioral interventions can help individuals take charge of their health. In this chapter, we examine the evidence backing various types of lifestyle modifications in the context of inflammation and pain and propose possible mechanisms for these effects.

The role of diet in pain stands to reason; supplying the body with building blocks for pro-resolution molecules such as specialized proresolving mediators (SPMs) may be of benefit. Certain diets may also contribute by reducing or promoting inflammation. Dietary interventions typically fall into three categories: restricting or eliminating particular types of food (e.g., low-fat diets, gluten-free diets, ketogenic diets, and vegetarian and vegan diets), altering total calorie intake, and supplementation via the addition of non-drug products (such as fish oil).

The benefit of exercise, however, may initially seem counterintuitive. It is widely accepted in the research field that pain is aversive, and that pain relief is rewarding (King et al. 2009; Navratilova et al. 2012). So why do so many people seek out strenuous exercise, and how can causing acute stress aid resolution? One well-known phenomenon of exercise is the "runner's high"; runners and many other athletes often report experiencing a brief period of euphoria after intense exercise. Endorphins, cannabinoids, and dopamine may be responsible for this phenomenon, and each of these has been separately tied to pain modulation. Still, the runner's high is just one of the many ways in which exercise interacts with the pain system. A wealth of studies suggest that exercise may contribute to the resolution of inflammation and the attenuation of pain by interacting with the immune system.

Despite the difficulties in implementing behavior change as medicine, the role of diet and exercise in chronic pain remains an important field of study. The mechanisms underlying these effects should be elucidated both to highlight the importance of healthy habits and to improve the field's understanding of protective and pro-resolution mechanisms.

13.2 Exercise, Inflammation, and Pain

Exercise can reduce inflammation and pain (Gleeson et al. 2011; Runhaar et al. 2019). Exercise has long been used in rehabilitation programs, especially for patients with chronic musculoskeletal conditions and chronic pain, and clinical

trials support this practice for patients with conditions such as low back pain or musculoskeletal pain (Tan et al. 2022; Van Middelkoop et al. 2010). In rodents, swim therapy has been found to alleviate the chronic pain caused by nerve injury. It was found in two studies that regular swim therapy sessions significantly reduced the mechanical allodynia and thermal hyperalgesia in both rats with chronic constriction injury (CCI) and mice with partial sciatic nerve ligation (PSNL) compared to animals receiving a control intervention (Shen et al. 2013; Kami et al. 2018). Rats with a spinal cord injury saw substantial improvements in mechanical allodynia after commencing either of swimming and treadmill training as compared to stand training or no intervention (Hutchinson et al. 2004). However, mice with chronic inflammatory and neuropathic pain exhibit deficits in voluntary wheel running as well as other movement-related assays (e.g., open field test, see Chap. 3). This presents a challenge: those who need exercise most may find their condition inhibitive.

Exercise is not just beneficial in resolving pain: it's also a powerful preventative measure. Correlational epidemiology repeatedly finds that those who are more active are less likely to develop a chronic pain condition (Law and Sluka 2017). This is consistent with the notion that long periods of sitting, as many experience in their day-to-day lives, can increase the excitability of pain pathways while decreasing the inhibitory effects of the central nervous system (CNS), making people who sit for long periods of time more susceptible to developing chronic pain. Conversely, regular exercise can decrease pain pathway excitability while increasing inhibitory effects in both the central nervous system and the immune system, powerfully reducing the risk of developing chronic pain. These ideas have led some experts to declare chronic pain to be, in part, a "disease of inactivity" (Sluka et al. 2018). This is also supported by animal research. Strikingly, six weeks of voluntary wheel running prior to nerve injury has been found to reduce the severity of pain and to hasten recovery in rats (Grace et al. 2016). A similar trend was found in mice allowed seven days of wheel running prior to establishment of chemotherapy-induced peripheral neuropathy (Slivicki et al. 2019).

The use of exercise, however, is very much a balancing act: the act of exercising can trigger pain in patients, which makes it difficult to continue exercise regimens during rehabilitation programs. Studies using animal models of exercise-induced pain suggest that activation of NMDA (N-methyl-D-aspartate) receptors in pain-modulating areas may be the cause of this pain; in other words, the induction of this pain follows a central mechanism (Sluka et al. 2018). A related concern is that some animal work has relied upon forced, not voluntary, exercise. Still, exposure to voluntary exercise has proven effective, even when animals exercised relatively little (Pitcher et al. 2017). In other words, even a little exercise may go a long way in helping relieve persistent pain. Extrapolating these data, it seems that encouraging chronic pain patients to partake in any degree of physical activity may be beneficial, even if their pain prevents them from engaging in strenuous exercise.

13.2.1 Release of Neurochemicals and Exerkines

The question remains: how does exercise exert these striking effects? One explanation points to the release of neurochemicals—some of which may be at the root of the "runner's high." Endorphins and endocannabinoids are two neuropeptides released during exercise. Dopamine may also be stimulated by voluntary exercise. Notably, these exercise-produced signaling molecules can serve as neuromodulators and inhibit pain in certain contexts (Pilozzi et al. 2020). They are best known for contributing to the phenomenon of the "runner's high," a brief feel-good period after intensive exercise (Boecker et al. 2008; Fuss et al. 2015). Endorphins, or "endogenous morphine" are named as such because they imitate the effects of morphine, by binding to morphine receptors. Twenty different kinds of endorphins exist; the one most tied to exercise is known as a beta-endorphin. Beta-endorphin is also released during acupuncture and meditation (Han 2003). Endorphins tend to be too large to cross the blood–brain barrier but may be endogenously produced in the CNS and travel via cerebrospinal fluid (Veening et al. 2012).

Like endorphins, endocannabinoids are endogenously produced and can create pleasurable feelings during exercise, in this case by acting on the endocannabinoid system. Unlike endorphins, endocannabinoids are small enough that they can cross the blood–brain barrier to reach the brain. In particular, endocannabinoids produce effects similar to tetrahydrocannabinol (THC), the main psychoactive component found in marijuana. Endocannabinoids are known to interact with sensory neurons and microglia through both the cannabinoid 1 receptors (CB1) and cannabinoid 2 receptors (CB2), respectively. Notably, CB2 is expressed in spinal cord microglia and activation of CB2 can induce an anti-inflammatory phenotype of microglia and inhibit neuropathic pain in rodents (Romero-Sandoval et al. 2009).

A third hypothesis is that exercise may release dopamine. Ventral tegmental area dopaminergic neurons are a critical part of the mesolimbic system. The exercised-induced hypoalgesia provided by voluntary wheel running has been tied to increased activation of the mesolimbic reward system (Kami et al. 2018). Recent studies using a range of exercise protocols suggest that central inhibitory mechanisms may play a role in the analgesic effect of exercise. Opioid, serotonin, and NMDA mechanisms in the rostral ventromedial medulla all increase exercise-induced analgesia (Lima et al. 2017).

The realization that skeletal muscle is an endocrine organ capable of secreting myokines (e.g., interleukin-6 [IL-6]), which participate in tissue and immune crosstalk, has provided a critical link between exercise and the health benefits it induces (Whitham and Febbraio 2016). These myokines are a subset of the exerkines released following exercise; there are cardiokines from heart, hepatokines from liver, adipokines from white adipose tissue, baptokines from brown adipose tissue, and neurokines from neurons. Based on these findings, exerkines are defined as a broad category of signaling moieties released in response to acute and chronic exercise, which exert their beneficial effects, including pain relief, through endocrine, paracrine and/or autocrine pathways and neuroimmune interactions (Chow et al. 2022).

These exerckines could interact with pain in numerous ways. Exercise triggers multiple endogenous protective and repair processes by altering gene expression and releasing a range of factors that prepare our body for the next challenge. These factors involve anti-oxidation, energy metabolism, and anti-inflammation. Oxidative stress can be triggered following an acute injury and cause secondary damage leading to chronic pain onset. Safakhah et al. examined whether exercise can reduce these secondary mechanisms after CCI in animals. They found that post-injury exercise not only reduced allodynia and hyperalgesia, but also increased ferric reducing ability of plasma (FRAP) and reduced TNF-alpha levels (Safakhah et al. 2017). Other ways in which exerkines may affect pain processing by inducing neuroplasticity and stimulating the secretion of BDNF (brain-derived neurotrophic factor) (Chow et al. 2022). Chronic pain is commonly thought of as maladaptive long-term potentiation (Ji et al. 2003); successful amelioration of SCI-induced allodynia via treadmill exercise in rats has been tied to increased BDNF transcription (Hutchinson et al. 2004). Still other exerkines may work to maintain brain homeostasis and confer protection against pathological insults by regulating glial activation and neuroinflammation. Activated microglia and multiple pro-inflammatory cytokines play active roles in the pathogenesis of pain as well as other neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD). It is safe to say that pain is not the only neurological condition improved by exercise. In the following section, we will explore how exerkines affect pain via crosstalk with the immune system.

13.2.2 Immune Crosstalk in Exercise–Induced Pain Modulation

In addition to its neuromodulatory effects, the anti-inflammatory effects of exercise are also well recognized and documented (Gleeson et al. 2011; Runhaar et al. 2019). Long-term exercise at low-to-moderate intensity beneficially regulates the inflammatory response (Mee-Inta et al. 2019). Nerve injury results in immune system activation leading to an increase in proinflammatory cytokines at both the location of injury and the spinal dorsal horn. Exercise has been found to stimulate macrophages to make a phenotypic switch, from a pro-inflammatory phenotype (M1) to an anti-inflammatory phenotype (M2) in uninjured muscle and, after a nerve injury and to promote the production of anti-inflammatory cytokines, contributing to an analgesic effect. Much of this effect is thought to be regulated via exerkine secretion.

The cytokine IL-6 was the first identified myokine, as skeletal muscle releases large amounts of IL-6 (Chow et al. 2022; Steensberg et al. 2000). Extensive research has shown that IL-6 can be both proinflammatory and anti-inflammatory in a context-dependent manner (Kistner et al. 2022). It was proposed that distinct signaling pathways (classic-signaling and trans-signaling) may mediate different effects of IL-6. The pro-inflammatory effects of IL-6 use trans-signaling by which IL-6 binds to a soluble form of IL-6 receptor. In contrast, the anti-inflammatory effects

of IL-6 are mediated by classic-signaling in which IL-6 acts on the membrane-bound non-signaling α-receptor. Notably, the levels of IL-6 may be reduced in several neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease.

Other myokines may also exhibit different anti-inflammatory properties. IL-6 upregulates the expressions of anti-inflammatory cytokine IL-10 and IL-1 receptor antagonist (IL-1Ra). IL-1Ra has a higher affinity for the IL-1R than IL-1α or IL-1β. Blocking the binding of IL-1 to its receptor interrupts the pro-inflammatory IL-1 signaling cascade and related microglial activity. It was found that long-term exercise can increase the production and secretion of IL-10 in the skeletal muscles and drives resident macrophages to take on an anti-inflammatory "M2" phenotype. This phenotypic shifting has also been observed in spinal cord microglia following exercise in a mouse model of neuropathic pain (Gong et al. 2017). Furthermore, inhibiting IL-10 blocked the benefit of wheel running in mice with musculoskeletal pain (Leung et al. 2016). These anti-inflammatory myokines can also be transported into the CNS from the peripheral circulation. Thus, exercise can alleviate pain by upregulation of the anti-inflammatory cytokines and inhibition of microglial activation in the spinal cord (Lesnak and Sluka 2020).

Recent evidence also points to the cytokine IL-4 as being an exerkine of critical importance in exercise-induced pain modulation. In a mouse model of peripheral nerve injury, two weeks of low-intensity exercise inhibited peripheral and central neuroinflammatory responses via upregulation of IL-4 (Bobinski et al. 2018). Moreover, treadmill exercise resulted in an increase in M2 macrophages and decrease in M1 macrophages, which secrete anti-inflammatory and inflammatory macrophages, respectively, in comparison to sedentary mice. Importantly, these results were not seen in IL-4 knockout mice. Furthermore, IL-4 has been found to contribute to pain amelioration by stimulating the secretion of endorphins from macrophages at the site of nerve injury (Celik et al. 2020), perhaps suggesting a link between exerkine and neuropeptide mechanisms.

13.2.3 Respiration and Circulation

Inflammation is notable for causing various breathing problems, perhaps most commonly seen in asthma, which affects over 20 million Americans. However, increased breathing rate and thus circulation can contribute to reducing inflammation following exercise. In general, decreased circulation reduces the body's ability to repair damaged tissues and protect tissues against further damage, as the body requires the flow of blood to deliver nutrients and carry away toxins, dead cells, and other debris. Thus, not only does increased inflammation impair circulation, poor circulation can also cause chronic inflammation. (Interestingly, as will be discussed later about the diet, nutrients found in nuts, seeds, olive oil, and oily fish can help improve circulatory health while inhibiting inflammation). One group, examining the role of improving heart circulation in mice as a method of treating coronary heart disease,

found that activating blood circulation could help inhibit inflammation (Ma et al. 2014).

Breathing during exercise can also activate the sympathetic nervous system. It is well established that the sympathetic and parasympathetic nervous systems control the heart rate. While the sympathetic nervous system releases catecholamines (epinephrine and norepinephrine) to accelerate the heart rate, the parasympathetic nervous system releases the hormone acetylcholine to slow the heart rate. Exercising for any duration increases heart rate, which will stay elevated for as long as the exercise is continued. At the beginning of exercise, the body removes the parasympathetic stimulation, which allows the heart rate to gradually increase. As exercise becomes more intensive, the sympathetic system acts to accelerate the heart rate even more. By contrast, regular cardiovascular exercise over an extended period of time is known to decrease your resting heart rate by increasing heart size, contractile strength, and length of time the heart fills with blood. This results in an increase in activity of the parasympathetic nervous system and decrease in sympathetic nervous system. In short, an accelerated heart rate, as seen in exercise, requires the use of the parasympathetic system to slow down.

The sympathetic nervous system has been linked to inflammation. The sympathetic system is well known for the "fight or flight" response. In addition, it is part of constant regulatory machinery that keeps body functions in a steady-state equilibrium. The sympathetic nervous system operates closely with the hypothalamic-pituitary axis (HPA) and the sensory nervous system and vagal nervous system (VNS), to accomplish its functions. When a pathogen enters the body, local activation of immune cells releases proinflammatory mediators, which are able to excite or sensitize (by lowering thresholds) of nociceptive afferent and vagal afferent nerve fibers. The inflammatory signals reach to the brain and result in activation of the two major stress axes, the HPA axis and the sympathetic nervous system. The proinflammatory cytokines IL-1β and TNF are crucial in this communication from the immune system to the central nervous system. In turn, central sympathetic activity also talks to the immune system, exhibiting direct effects on inflammatory cytokines. In a study with hypertensive patients, central inhibition of the sympathetic nervous system decreased peripheral TNF serum levels. Similarly, stress responses that modulate sympathetic nervous system activity have a great impact on inflammation. However, there might be a disruption of this communication between the brain and the immune system in the course of protracted inflammation, as shown in an arthritis model in rats. Thus, the activation of the sympathetic nervous system during exercise may also influence inflammation through the increased sympathetic nervous system activity (Wei et al. 2020).

Exercise has also been shown to benefit people with knee osteoarthritis. Subchondral bone degeneration and synovitis are the main characteristics of knee osteoarthritis, which can be exacerbated with mechanical overload, inflammation, factors involving metabolism or hormones and aging. Although surgery for knee osteoarthritis is available, it tends to be for patients with end-stage knee osteoarthritis only. As such, exercise becomes an important part of treatment for those with knee osteoarthritis. Exercise can not only inhibit inflammation and further

degeneration of cartilage, it can also stop the loss of subchondral bone and metaphyseal bone trabeculae. According to recent studies, pain, stiffness, joint dysfunction, and muscle weakness are also improved with exercise in patients with knee osteoarthritis. Varied forms of exercise, including aerobic exercise, strength training, neuromuscular exercise, balance training, proprioception training, aquatic exercise, as well as traditional exercise can all provide benefits, such as reduced inflammation, delayed cartilage and bone degeneration, and improved tendon and muscle structure (Zeng et al. 2021).

The mechanisms by which exercise helps prevent the exacerbation of chronic inflammatory diseases requires further elucidation. One study has shown that exercise can promote resolution of acute inflammation by increasing levels of resolvin D1 and macrophage phagocytic activity. The study found that mice given a four-week treadmill exercise regimen had higher RvD1 and macrophage phagocytic activity levels. They also found that neutrophil clearance occurred earlier after acute inflammation. The authors further determined that exercise may achieve these effects through the release of epinephrine, which is known to have immunomodulatory effects. Macrophages treated with epinephrine show higher levels of RvD1 and 15-lipoxygenase-1 abundance. These changes were prevented by incubation with the α1 adrenergic receptor (α1-AR) antagonist prazosin. It was found that stimulation of α1-AR with phenylephrine also enhanced RvD1 production and macrophage phagocytosis. During acute inflammation, prazosin abrogated exercise-enhanced neutrophil clearance, macrophage phagocytosis, and RvD1 biosynthesis. These results point to the possibility that exercise-stimulated epinephrine enhances resolution of acute inflammation in an α1-AR-dependent manner (Zheng et al. 2019).

Of particular interest is a study from Harvard Medical School reported that stretching can impact inflammation resolution. Tissue stretching was shown to activate local pro-resolving mechanisms in the acute phase of inflammation. In a rat model of inflammation induced by carrageenan, stretching was shown to reduce edema and neutrophil count and increase RvD1 concentrations within inflamed tissue. Interestingly, subcutaneous resolvin administration could recapitulate the action of stretching. The *in vivo* effects can be reproduced in ex vivo conditions, which demonstrated that stretching of connective tissue was sufficient to inhibit the migration of neutrophils and enhance tissue RvD1 concentration (Lisbeth Berrueta et al. 2016).

Another study characterized the inflammatory lipid mediator response in blood to unaccustomed resistance exercise in humans. It was found that acute proinflammatory signaling is mechanistically linked to the induction of an active resolution program, regulated by proresolving lipid mediators during post-exercise period of recovery. Postexercise recovery was characterized by elevated levels of cyclooxygenase (COX)-derived prostanoids, lipoxygenase-derived leukotrienes, as well as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)-derived resolvins (RvD1 and RvE1), and protectins. Notably, Ibuprofen, an anti-inflammatory treatment, not only blocked the exercise-induced prostanoids but also suppressed the

SPM response (Markworth et al. 2013). Thus, exercise-induced acute inflammation may have beneficial effects by promoting SPM production and signaling.

13.3 Diet in Inflammation and Pain

Diet also plays a significant role in modulating inflammation. Microbiota and its metabolites have been shown to alter CNS function. Probiotics restore the eubiosis in the gut while a gluten-free diet, by modulation of microbiota profile and intestinal permeability, can alter the activity of microbiota-gut-brain axis, which was associated with the pathogenesis of depression. Of note is that microbiota being able to digest gluten may play a role in the formation of peptides with different immunogenic capacities. It was found that the combination of a gluten-free diet and probiotic supplementation may inhibit the immune-inflammatory cascade in major depression disorder, improving both psychiatric and gut barrier-associated features (Karakula-Juchnowicz et al. 2019).

Gluten-related disorders include Celiac disease (CD) and non-celiac gluten/wheat sensitivity (NCG/WS). Both are triggered and worsened by ingestion of gluten proteins. Other components, such as amylase/trypsin inhibitors and fermentable oligosaccharides, disaccharides, monosaccharides and polyols, may also play a role in the development of NCG/WS onset. The only effective treatment to date is a lifelong adherence to a strictly gluten-free diet. Emerging evidence shows the involvement of intestinal barrier which regulates the delicate crosstalk between metabolic, neuroendocrine, and immunological functions. Especially, the microbiota plays a crucial role in regulating the gut integrity and inflammation process, which is associated with the outbreak of CD and NCG/WS (Caio et al. 2020).

In NOD/ShiLtJ (NOD) mice, in which leukocytes infiltrate pancreatic islets to produce insulitis, a lifelong gluten-free diet was found to decrease infiltration of monocytes/macrophages and T cells in salivary glands, leading to reduced inflammation in pancreatic islets. Thus, autoimmune diseases, such as type 1 diabetes (T1D) and Sjogren's syndrome (SS), may be alleviated by a gluten-free diet (Haupt-Jorgensen et al. 2022).

Omega-3 polyunsaturated fatty acids (PUFAs) are enriched in healthy diet and fish oil and demonstrate a wide range of benefits in human health and animal disease models. PUFAs include eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and docosahexaenoic acid (DHA). It is generally believed that many of the biological functions of PUFAs are mediated via bioactive metabolites, produced by the actions of fatty acid oxygenases, including cyclooxygenases, lipoxygenases, and cytochrome P450 monooxygenases (Ishihara et al. 2019).

In a clinical trial with EPA intervention, icosapent ethyl (the ethyl ester form of EPA) demonstrates a significant improvement of cardiovascular events. Importantly, EPA is a precursor for the formation of E series of resolvins, which belong to a

subfamily of specialized proresolving mediators (SPMs). Resolvin E1 (RvE1) is the best investigated member of E series of resolvins. It stimulates the resolution of inflammation and reduces atherosclerosis through its specific receptor ChemR23 (also named ERV1). Furthermore, ω-3 fatty acids produce additional benefits by decreasing the levels of proinflammatory and proatherosclerotic leukotrienes. Interestingly, the ratio of resolvins and leukotrienes is an emerging marker of resolving vs. non-resolving vascular inflammation. SPMs was shown to alleviate atherosclerosis independently of changing cholesterol and triglyceride levels. The findings of the recent clinical trials of ω-3 fatty acid supplementation have demonstrated the importance of the type and dose of ω-3 supplementation. They also highlight the need for risk stratification in terms of patient selection for ω-3 supplementation for prevention of primary and secondary cardiovascular diseases (Back et al. 2019).

Diet can have a profound impact on both inflammation and pain. One diet that has been popularized as a method of reducing inflammation is the omega-3 diet. Omega-3 fatty acids are also known as "essential fats" because they cannot be produced in the human body and thus must be obtained through food. These fats can be divided into three groups: alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). ALA can be found in various nuts, such as walnuts, and many plants. EPA and DHA can both be found in cold-water fish, including salmon and tuna. This section explores the effects of omega-3 fatty acids and diets including these fats on inflammation and pain.

PUFAs have been found to be analgesic (Bjørklund et al. 2019). EPA and DHA are essential precursors for the biosynthesis of SPMs, which includes resolvins, protectins, and maresins (Ji 2023; Serhan 2014). These mediators all act as potent analgesics in various animal models of pain, including inflammatory, post-operative, and neuropathic pain models. Resolvins can powerfully suppress inflammatory pain. They are 1000 times more effective than EPA and DHA precursors found in food items and 100 times more effective than morphine. These mediators not only resolve inflammation, but also suppress neural plasticity, glial function, and TRP (transient receptor potential) channel function (Ji 2023). Previous studies have found fish oil diets to be ineffective for treating migraines and rheumatoid arthritis. In these studies, however, it is ambiguous whether or not the PUFAs from the diets were transferred to the patients in any significant way. In another study, in which PUFAs were directly administered to patients suffering from migraines, patients saw significant reductions in pain, supporting the effectiveness of PUFAs in suppressing pain (Van De Ven and Ji 2013).

Another diet known to reduce inflammation is the ketogenic diet, which consists of high-fat, low carbohydrate food that causes cells to rely on ketone rather than glucose for energy. The ketogenic diet has been shown to be effective in treating pediatric epilepsy and type II diabetes, and may potentially even reduce brain injury. The cellular mechanisms enabled by a dependence on ketone suggest that the ketogenic diet may be able to reduce pain and inflammation. One study found a significant reduction in inflammation in rats given a ketogenic diet, based on hindpaw swelling and plasma extraversion measurements. In addition, the diet resulted in

thermal hypoalgesia. As such, the ketogenic diet may be another option for reducing inflammation via diet (Ruskin et al. 2009).

Another study examined the effects of a meat-, gluten-, and lactose-free diet in rheumatoid arthritis patients. They found that the diet reduced the number of circulating leukocytes and neutrophils, as well as the level of hs-C-Reactive Protein after three months, suggesting that such a diet may help further control inflammation in rheumatoid arthritis patients who already have proper drug treatments in place (Guagnano et al. 2021).

Conversely, some diets can also contribute to inflammation. The stereotypical "western diet," full of processed oils and fats, and known for promoting obesity, has been identified as a diet that can promote inflammation through omega-6 PUFAs. Omega-6 PUFAs can be found in many vegetable oils, such as sunflower, corn, soybean, and cottonseed oils. These PUFAs can build up in membrane phospholipids, then oxidize into pronociceptive oxylipins to induce pain. In mice, omega-6 PUFAs have been found to induce peripheral neuropathy, perhaps explaining the neuropathy found in many obese but non-diabetic people (McGinnis and Ji 2021). In particular, mice administered an ω-6 PUFA-enriched diet develop lasting hypersensitivity, develop persistent spontaneously active and hyper-responsive glabrous afferent fibers, and histologic markers of peripheral nerve damage characteristic of peripheral neuropathy. Moreover, omega-6 PUFAs, such as linoleic and arachidonic acids, build up in lumbar dorsal root ganglia and can be allowed to move more easily by phospholipase PLA2 activity. Omega-6-induced peripheral neuropathy is reversible, however, by either inhibiting platelet-activating factor acetylhydrolase (PLA2G7) or with a diet rich in omega-3 PUFAs. These treatments can reduce nociceptive behaviors, neurophysiologic abnormalities, and afferent histopathology induced by high omega-6 consumption in mice. Omega-6 PUFA accumulation also worsens allodynia found in preclinical inflammatory and neuropathic pain models, which is highly correlated with many pain indices of clinical diabetic neuropathy (Boyd et al. 2021).

13.4 Conclusions and Future Directions

This chapter examined the benefits of exercise and diet in terms of reducing inflammation and pain. During exercise, the release of neurochemicals (i.e., endorphins and endocannabinoids) and increased respiration and circulation can help reduce inflammation. Over time, exercise can also contribute to altering fat composition, increasing brown fat while decreasing white fat, which is associated with inflammation. Moreover, exercise results in release of epinephrine and IL-6, which can promote SPM levels and phagocytic activity by macrophages to resolve inflammation. Exercise is particularly helpful to those with knee osteoarthritis, which otherwise impairs mobility and decreases quality of life.

Diet can also play an important role in reducing inflammation, with omega-3 PUFAs, found in fish oil, containing precursors for a variety of SPMs, all of which help resolve pain and inflammation. High-fat, low-carbohydrate ketogenic diets and meat-, gluten-, and lactose-free diets were also shown to decrease inflammation. On the other hand, omega-6 PUFAs, often found in vegetable oils used in high-fat "western" diets which promote obesity, increase inflammation, leading to painful peripheral neuropathy. The effects of omega-6 PUFAs, however, can be reversed via the administration of omega-3 PUFAs.

The anti-inflammatory effects of both exercise and omega-3 diets may depend on SPMs. SPMs consist of cell signaling molecules that are produced via the metabolism of PUFAs by one or several of the enzymes, including lipoxygenase, cyclooxygenase, and cytochrome P450 monooxygenase. SPMs have potent anti-inflammatory and neuroprotective capabilities. As mentioned before, SPMs consist of resolvins, protectins, and maresins and possess potent analgesic actions in various animal models (Ji 2023). Exercise and diets can effectively change immune cell phenotypes and contribute to the resolution of inflammation and pain. We highlight that a combination of exercise and a healthy diet can facilitate the biosynthesis of SPMs from omega-3 PUFAs, leading to synergistic health benefits (Figs. 13.1 and 13.2).

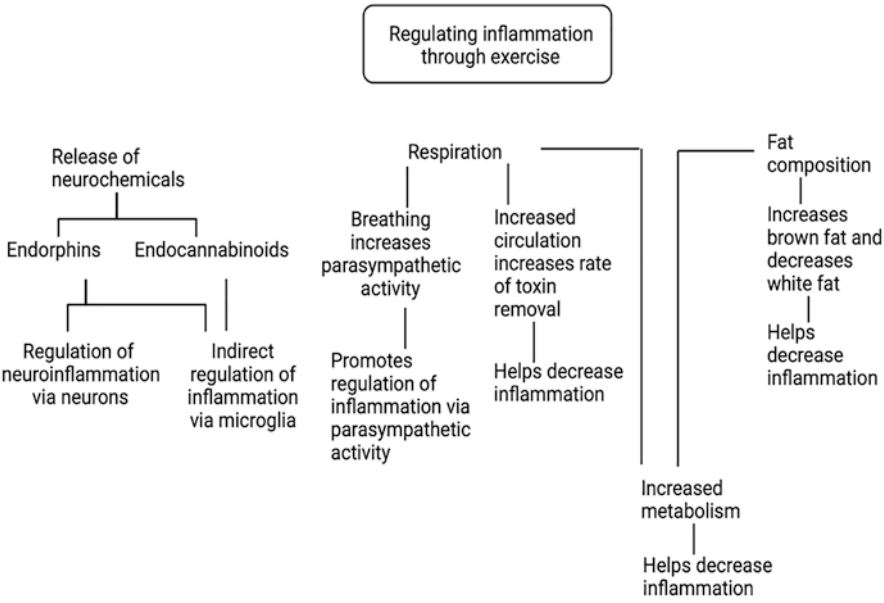

Fig. 13.1 Regulation of inflammation through exercise. Exercise can help regulate inflammation through a variety of processes, including the release of neurochemicals, respiration, and changing fat composition. The latter two processes contribute to increased metabolism. In such a way, exercise is able to promote the regulation of inflammation in various ways, leading to pain relief

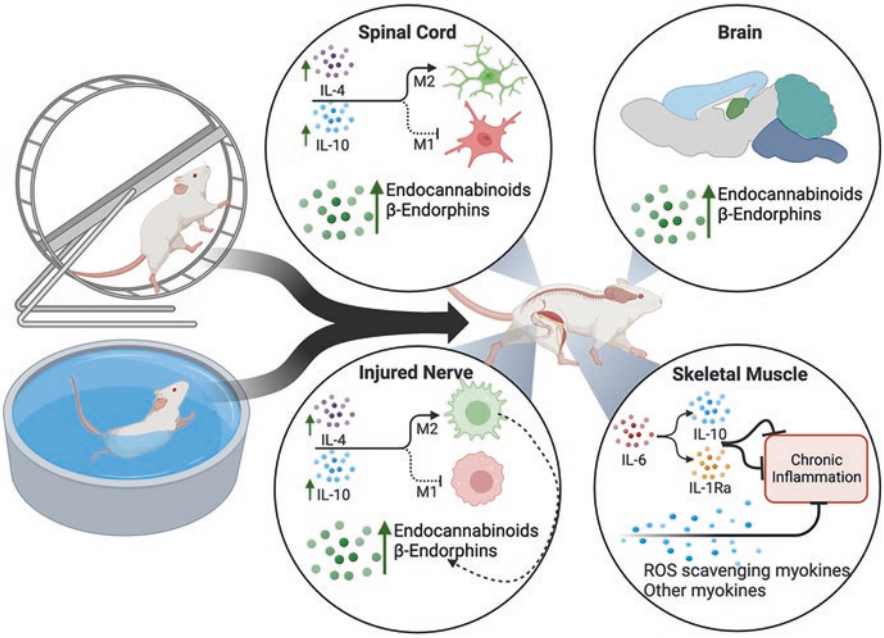

Fig. 13.2 Effects of exercise on a nerve-injured rodent. Exercise drives pain relief at multiple levels. In all nervous tissues (nerve, spinal cord, and brain), endocannabinoids and β-endorphins modulate neuronal activity. IL-4 and IL-10 drive microglia toward an anti-inflammatory phenotype in the spinal cord and macrophages toward a similar phenotype near the injured nerve. In skeletal muscle, IL-6 drives secretion of IL-10 and IL-1Ra, contributing along with other myokines toward reduction of chronic inflammation and chronic pain

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